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Vinke, Joanna Sophia J; Heerspink, Hiddo J L; de Borst, Martin H

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REVIEW

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Effects of sodium glucose cotransporter 2 inhibitors on mineral metabolism in type 2 diabetes mellitus

Joanna Sophia J. Vinke[a], *Hiddo J.L. Heerspink*[b], *and Martin H. de Borst*[a]

Purpose of review
Sodium glucose cotransporter 2 (SGLT2) inhibitors are relatively novel antidiabetic drugs that improve glycemic control and reduce cardiovascular outcomes as well as renal function decline. SGLT2 inhibitors act by inhibiting glucose reabsorption in the proximal tubule of the kidney. Emerging data suggest that these drugs may also influence bone and mineral metabolism. This review summarizes clinical trial data on bone and mineral outcomes, and discusses potential underlying mechanisms.

Recent findings
Three large randomized controlled trials documented cardiovascular and renal protective effects of SGLT2 inhibitors. Recent studies indicate that SGLT2 inhibitors influence renal phosphate reabsorption and calciuria. Although the CANVAS trial suggested an increased fracture risk associated with canagliflozin compared with placebo, the vast majority of trials and meta-analyses did not demonstrate an increased fracture risk associated with SGLT2 inhibitor use.

Summary
SGLT2 inhibitors have shown clinically relevant cardiovascular and renal protective effects. The long-term implications for bone health, in particular in the context of chronic kidney disease, are still incompletely understood and warrant further investigation.

Keywords
bone mass density, fibroblast growth factor 23, kidney, phosphate, sodium glucose cotransporter 2 inhibitors

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic diseases worldwide, affecting an estimated 422 million adult patients in 2014 [1]. Since 1980, its prevalence has increased from 4.7 to 8.5% in adults [1]. Diabetes was the cause of 1.5 million deaths in 2012 [1]. Type 2 diabetes mellitus (T2DM) is one of the most common causes of chronic kidney disease, and a major risk factor for cardiovascular disease.

Recently, promising new drugs have been introduced for the treatment of T2DM, including sodium glucose cotransporter 2 (SGLT2) inhibitors, dipeptidylpeptidase-4 (DPP4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. SGLT2 inhibitors have shown clinically relevant improvements in cardiovascular outcomes and slower progression of chronic kidney disease, especially in populations with established cardiovascular disease. Recent data from small trials suggest that SGLT2 inhibitors may influence bone and mineral metabolism. Here, we will first review the most important data from cardio-renal outcome studies with SLGT2 inhibitors. Subsequently, we will focus on their potential effects on bone and mineral metabolism.

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS: MECHANISMS OF ACTION

Sodium-glucose cotransporters 1 (SGLT1) in intestinal cells are essential for the absorption of dietary glucose and galactose. SGLT2 cotransporters are predominantly expressed in the proximal tubule in the kidney, and reabsorb sodium and glucose in collaboration with glucose transporters (Fig. 1)

[a]Division of Nephrology, Department of Internal Medicine and [b]Department of Clinical Pharmacology and Pharmacy, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Correspondence to Dr Martin H. de Borst, MD, PhD, Division of Nephrology, Department of Internal Medicine, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, the Netherlands. Tel: +31 50 361 6161; fax: +31 50 361 9350; e-mail: m.h.de.borst@umcg.nl

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KEY POINTS

- SGLT2 inhibitors improve cardiovascular and renal clinical outcomes.
- SGLT2 inhibitors might interfere with renal phosphate reabsorption and induce calciuria.
- Some studies have suggested an increased fracture risk associated with SGLT2 inhibitors, although the vast majority of clinical trials and meta-analyses do not show an increased fracture risk.

[2]. By blocking SGLT2 cotransporters, SGLT2 inhibitors induce glucosuria and therefore have a strong glucose-lowering effect. Furthermore, osmotic diuresis results in a decrease in blood pressure. Currently, three SGLT2 inhibitors are available: empagliflozin and dapagliflozin selectively suppress the activity of SGLT2, whereas canagliflozin also has some SGLT1-inhibiting properties.

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS: CLINICAL OUTCOMES

In a number of trials, all SGLT2 inhibitors led to statistically significant reductions in body weight, varying between an average decline of 1.6 kg with canagliflozin, and a decline of 2.4 kg with dapagliflozin, compared with placebo [2–4,5▪,6,7,8▪,9]. Furthermore, SGLT2 inhibitors reduced systolic and diastolic blood pressure [5▪,6,7]. In the CANVAS trial, a large randomized controlled trial (RCT) of 10 142 participants with T2DM, canagliflozin led to a further glycosylated hemoglobin (HbA1C) reduction by 0.58%, compared with placebo [7]. The beneficial effects of SGLT2 inhibitors on cardiovascular outcomes in high-risk populations are summarized in Fig. 2. The composite outcome of major cardiovascular events (MACE: cardiovascular mortality, nonfatal myocardial infarction or nonfatal cerebro-vascular events) occurred significantly less frequently with canagliflozin compared to placebo [Hazard Ratio (HR) 0.86; 95% confidence interval (CI) 0.75–0.97; P=0.02 for superiority] in T2DM

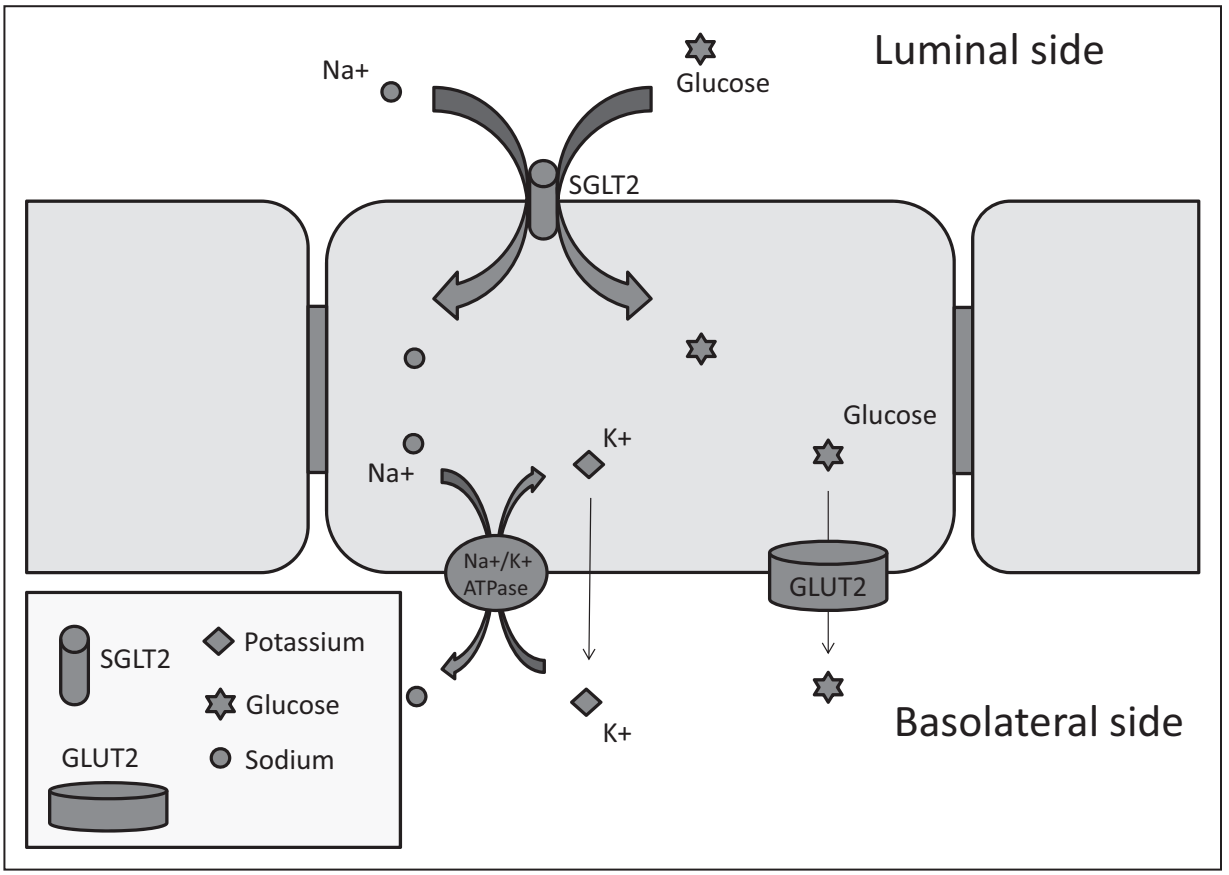

FIGURE 1. Sodium-glucose cotransporter 2 (SGLT2) in the renal tubule. SGLT2 reabsorbs sodium (Na+) and glucose from the luminal side of the proximal renal tubule. On the basolateral side of the cell, glucose is exported into the circulation by glucose transporters (GLUT2). The intracellular sodium gradient, crucial for SGLT2 function, is maintained by the active Na+/K+ ATPases. Potassium can passively cross the cell membrane back into the circulation.

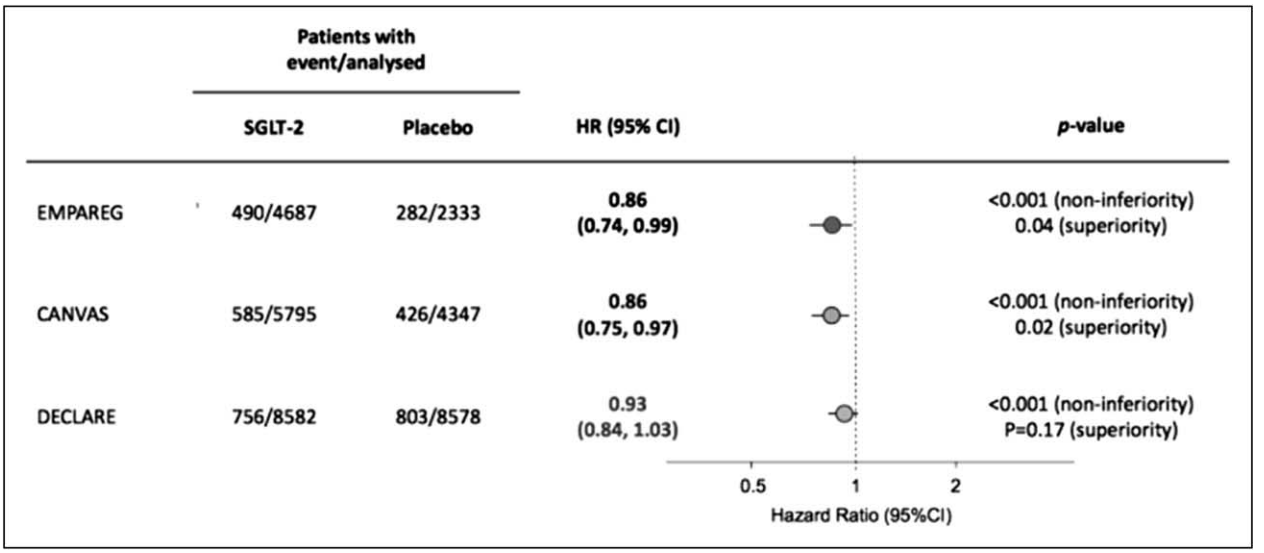

FIGURE 2. Effects of sodium glucose cotransporter 2 inhibitor on cardiovascular events in patients with type 2 diabetes mellitus and increased cardiovascular risk. The EMPAREG trial and the CANVAS trial showed a significant reduction in MACE (cardiovascular mortality, non-fatal myocardial infarction or non-fatal cerebro-vascular events) of empagliflozin and canagliflozin, respectively. In the DECLARE trial however, the reduction in MACE was not significant with dapagliflozin. HR, hazard ratio; 95% CI, 95%, 95% confidence interval.

patients with increased cardiovascular risk [7]. In the EMPAREG OUTCOME trial, an RCT with 7020 patients with T2DM and preexisting cardiovascular disease, empagliflozin provided similar results on cardiovascular events (HR 0.86 compared with placebo; 95% CI 0.74–0.99, $P = 0.04$ for superiority) [6]. In the DECLARE trial, an RCT comparing dapafliglozin with placebo in 17 160 diabetic patients with atherosclerotic cardiovascular disease, the difference in MACE did not reach statistical significance (HR 0.93; 95% CI 0.84–1.03; $P = 0.17$ for superiority), although patients in the dapagliflozin group had a 0.42% (95% CI; 0.40–0.45) greater reduction in HbA1C compared to patients in the placebo group [5▪]. Long-term effects of SGLT2 inhibitors on HbA1C are more sustainable than with DDP4 inhibitors and sulfonylurea derivates [10].

SGLT2 inhibitors also have beneficial effects on the kidney [11▪]. Canagliflozin significantly retarded the progression of albuminuria, and empagliflozin slowed down renal function decline [7,12].

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS: ADVERSE EFFECTS

The adverse effects of SGLT2 inhibitors are generally mild. Genital infections, such as balanitis and vulvovaginitis, are the most common adverse events, caused by increased urinary glucose concentrations [5▪,6,7,8▪,10]. A higher incidence of diabetic ketoacidosis has been reported, especially in off-label use of SGLT2 inhibitors in type 1 diabetic patients, but also in T2DM [5▪,10].

SGLT2 inhibitors do not increase the risk of hypoglycemia [6,7,8▪]. In the DECLARE trial, dapagliflozin was even associated with a lower risk of hypoglycemia than placebo (HR 0.68, CI 0.49–0.95, $P = 0.02$) [5▪]. Because of their mechanism of action, SGLT2 inhibitors decrease circulating volume and sodium. This may be beneficial for diabetic patients with hypertension but may also lead to hypotension.

Participants of the CANVAS study who received canagliflozin had an increased incidence of volume depletion as a result of osmotic diuresis and natriuresis (26 events per 1000 patient years with canafliglozin versus 18.5 events with placebo, $P = 0.009$) [7]. A meta-analysis of eight other RCTs showed a trend toward an increased risk of complications from volume depletion with canagliflozin compared to placebo (HR 1.13, CI 0.74–1.73 with 100 mg; HR 1.45, CI 0.98–2.13 with 300 mg) [13]. In contrast, a number of individual studies comparing SGLT2 inhibitors with placebo did not observe an increased risk of hypovolemia [4,5▪,6,8▪,9]. Furthermore, in the CANVAS trial, a higher incidence of amputations of the lower extremities has been reported (HR 1.97, 95% CI 1.41–2.75) [7] In contrast, a similar signal was not observed in the DECLARE trial: the amputation rate was similar to placebo [5▪].

EFFECT OF DIABETES ON BONE AND MINERAL METABOLISM

T2DM in itself is accompanied by an increased bone mass density (BMD). This is most likely related to anabolic effects of hyperinsulinism, lower bone turnover and, generally, a higher BMI [3,14]. Paradoxically, diabetic patients have a higher risk of fractures compared to nondiabetic controls with the same BMD score [15]. This discrepancy may be partly explained by a higher fall risk, for example due to diabetic neuropathy, but also several metabolic processes and antidiabetic medications impairing bone quality are likely involved. In diabetes, storage of advanced glycation end products such as pentosidine in collagen stiffens the structure of extracellular matrix, making it more brittle and prone to fractures [3,14,16]. Furthermore, osteoblast activity can be inhibited by hyperglycemia or thiazolidinediones [3,17,18]. Thiazolidinediones, which also cause bone resorption, are well known to reduce BMD and are associated with an increased fracture risk [18–20]. Insulin may result in hypoglycemia, increasing the risk of falls. In contrast, metformin stimulates osteoblast activity and incretin-based therapies (DPP4 inhibitors and GLP-1 analogues) have an anabolic effect on bone formation [20,21].

EFFECTS OF SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS ON CIRCULATING MARKERS OF MINERAL METABOLISM

Classical physiological research performed in the early 1980s, long before SGLT2 was cloned, already suggested a mechanistic link between sodium-glucose transport across the proximal tubular membrane and mineral metabolism. In isolated renal cortices of rabbits, the authors found that the transporters of phosphate, glucose and alanine all made use of the same sodium gradient, thereby limiting each other [22]. Because SGLT2 inhibitors prevent the cotransport and reabsorption of sodium and glucose, the sodium gradient is preserved for the sodium-dependent phosphate transport proteins IIa (NaPi IIa, SLC24A1) and IIc (NaPi IIc, SLC34A3), stimulating phosphate reabsorption at the proximal tubule. These mechanistic studies were recently further substantiated by two human studies with SGLT2 inhibitors. In a single-blinded randomized cross-over study with 25 healthy volunteers who received either canagliflozin or a placebo during 5 days, canagliflozin was associated with glucosuria [23▪▪]. During the first day, a transient but marked increase in sodium excretion was observed in correlation with a significant rise in serum phosphate. These findings support the theory of phosphate retention induced by an enforced sodium gradient. Calcium excretion increased slightly without causing any changes in serum calcium. A probable cause of increased calcium excretion is the high tubular flow as a result of osmotic diuresis, reducing paracellular calcium reabsorption in the proximal tubule and reducing the calcium gradient between the tubule and the medullar interstitium [24]. In children with a genetic SGLT2 deficiency, familial renal glucosuria, hypercalciuria is also a well-known phenomenon [25].

Interestingly, serum fibroblast growth factor 23 (FGF23) also increased in correlation with phosphate in the volunteers during canafliglozin treatment [23▪▪]. FGF23 is a phosphaturic hormone that is excessively increased during progression of renal function loss, and it is known for its adverse extrarenal effects on the heart [26▪]. FGF23 is secreted by osteocytes in response to intestinal phosphate absorption by an unknown mechanism of phosphate-sensing, acting to prevent a positive phosphate balance. Apart from inhibiting phosphate reabsorption from the proximal tubule by downregulating NaPi IIa transporters, FGF23 lowers phosphate levels in two different ways: by the suppression of parathyroid hormone (PTH) secretion, reducing phosphate release from bone, and by inhibiting 1-α-hydroxylase, slowing down the conversion of 25-hydroxycholecalciferol into active vitamin D, or 1.25-dihydroxycholecalciferol. In turn, 1.25-dihydroxycholecalciferol stimulates phosphate uptake from the intestine. Indeed, the 1.25-dihydroxycholecalciferol levels of the participants who received canagliflozin persistently declined [23▪▪]. PTH, on the other hand, increased, most likely as a result of the fall in vitamin D and loss of calcium. The association of canagliflozin use with a rise in serum phosphate has been confirmed in clinical studies with diabetic patients [2,27,28]. Also, in diabetic mice, canagliflozin increased urinary calcium excretion and serum FGF23 levels [29,30,24].

Similar results were obtained in a posthoc analysis of the IMPROVE trial in patients with T2DM and albuminuric kidney disease, in which dapagliflozin was compared to placebo [31▪▪]. During dapagliflozin treatment, serum phosphate levels increased by 9% and PTH by 16% compared to placebo. FGF23 also significantly increased with 19% [31▪▪]. Other studies using dapagliflozin confirmed most of these findings, although an increase in PTH could not be reproduced in a trial with diabetic patients with different renal functions [3,9]. In conclusion, SGLT2 inhibitors may increase PTH levels, induced by calciuria, and increase FGF23, provoked by increased phosphate reabsorption, concertedly decreasing active vitamin D.

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS AND THEIR EFFECTS ON BONE TURNOVER MARKERS

Bone quality is mainly determined by bone turnover, or the rate of bone degradation by osteoclasts and bone synthesis by osteoblasts. Bone turnover markers are rapidly responding biomarkers of skeletal remodeling with a high interindividual variability [27]. Deregulated bone resorption markers are associated with an increased fracture risk [32]. Some effects of SGLT2 inhibitors on bone turnover markers have been documented. In diabetic mice, the bone resorption marker RatLAPs was increased compared to control mice [29,30]. Although insulin therapy attenuated this deviation, canagliflozin further increased RatLAPs [29,30]. Reduced levels of procollagen type 1 N-terminal propeptide (P1NP), a bone formation marker, in diabetic mice compared to control mice were only seen in one of two studies by the same group, and there was no clear effect of canagliflozin on this marker [29,30].

In clinical studies with diabetes type 2 patients, canagliflozin increased the bone-resorption marker collagen type 1 β-carboxytelopeptide (CTX) in correlation with weight loss and, in postmenopausal women, with a decline in osteoclast inhibiting estradiol [16,33]. Osteocalcin, a small bone-specific protein correlated with bone formation, significantly increased [16,33]. However, there was no evidence of any effect of dapagliflozin on P1NPor CTX [3,4].

There is no evidence that these alterations in bone turnover markers can be the result of direct binding of SGLT2 inhibitors to bone tissue. No expression of SGLT2 was observed in mouse calvarian osteoblasts, bone marrow macrophages, preosteoclasts or mature osteoclasts [30]. Another study in rodents reported no expression of SGLT2 in skeletal tissue or any other extrarenal tissues [34]. Finally, no binding of intravenously injected 4-fluoro-dapagliflozin was observed in bone tissue of rats or mice [35]. Although SGLT2 is highly specific to the kidney, SGLT1 is also expressed in the heart, lung, biliary tract, prostate, salivary gland, trachea, colon, small intestine and in skeletal muscle tissue [36–40]. To our knowledge, only one study analyzed SGLT1 expression in bone, which was not detected [30]. Thus, we consider it unlikely that canagliflozin, which has some SGLT1 inhibiting properties as well, could have direct off-target effects on bone.

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS, BONE MASS DENSITY AND FRACTURE RISK

The alterations in bone turnover markers associated with canagliflozin and the rise in PTH and decline in vitamin D as a result of all SGLT2 inhibitors may raise the question whether such effect would translate into an increased fracture risk. Moreover, SGLT2 inhibitor-induced weight loss, which is associated with a reduced BMD by lowering mechanical forces on bone tissue, may be an additional factor compromising bone quality. Especially in women, in whom weight loss attenuates the activity of aromatases resulting in lower estradiol levels, the bone density and turnover can be severely affected [2,33,41].

Canagliflozin

The large CANVAS RCT reported an increased incidence of fractures with canagliflozin, which forced the Food and Drug Administration to release a Drug Safety Communication and update the drug label [7] https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm. In the canagliflozin group, 15.4 fractures were observed per 1000 patient years, compared to 11.9 fractures in the placebo group (HR 1.26; 95% CI 1.04–1.52). Specifically, the incidence of fractures that occurred in the distal extremities was increased. Remarkably, when only fractures at sites known to be at risk for osteoporosis-related fractures were considered, the difference was no longer significant.

Another RCT comparing canagliflozin to placebo in 716 patients with diabetes mellitus type 2 revealed a small but significant decrease in hip BMD in canagliflozin, which was partially explained by weight loss [33]. The BMD of the lumbar spine, femur and arm was not compromised. In a large cohort study comparing 79 964 patients with T2DM who received canagliflozin with 79 964 similar patients who received a GLP-1 agonist, there was no significant difference in the occurrence of fractures between both groups [42▪].

A meta-analysis of nine RCT showed a significantly increased fracture risk with canagliflozin compared to placebo, glimepiride or sitagliptine [13]. However, the CANVAS trial was by far the largest study in this analysis and therefore importantly influenced the overall results. The CANVAS trial participants were on average older than participants from the other trials: 6.7% of CANVAS participants were over 75 years, compared to 3.7% of participants of the other trials [13]. It is therefore plausible that the a-priori fracture risk was higher in the CANVAS trial.

In rats, long-term canagliflozin treatment led to adverse effects on trabecular bone [29].

Dapagliflozin

In the DECLARE trial comparing the incidence of cardiovascular events in dapagliflozin and placebo

in 17 160 T2DM patients, the fracture risk was similar in both study arms [5▪]. A cohort study involving 22 618 T2DM patients with a mean follow-up of 12 months showed also no association between dapagliflozin use and the risk of fractures [43]. Ljunggren *et al.* [3] and Bolinder *et al.* [4] measured BMD in another RCT comparing 182 diabetic patients who were all overweight and received either dapagliflozin or placebo. DEXA scans of the lumbar spine, femoral neck and hip were performed after 50 weeks of follow-up and no significant differences in BMD or the incidence of fractures between the two groups were found [3,4]. Only one smaller RCT comparing dapaglifozin with 252 participants with diabetic nephropathy showed a clear relation between dapagliflozin and fractures: 7.7% of the patients in the active treatment arm reported a fracture during 104 weeks of follow-up, compared to none of the patients who received placebo [9].

Empagliflozin

In the EMPAREG-outcomes trial, there were no indications that empagliflozin-treated patients had a higher risk of fractures, with an incidence of 3.7–3.9% depending on the dose compared to 3.9% in the placebo group [6].

Four meta-analyses comparing the use of any SGLT2 inhibitor with placebo or other control treatments in tens of thousands of patients, including a Cochrane review in patients with diabetic kidney disease, did not confirm the relationship between SGLT2 inhibitor use and an increased fracture risk [8▪,44–46].

CONCLUSION

SGLT2 inhibitors are a new class of antidiabetic drugs that have demonstrated significant improvements in glycemic parameters and cardiovascular and renal outcomes in patients with T2DM. Although a reduced BMD and increased risk of fractures have been observed in a limited number of studies with canagliflozin and dapagliflozin, this has not been confirmed by large meta-analyses and multiple other trials suggesting that any signals observed in a few studies are likely to be chance findings. Mechanistic studies suggest that SGLT2 inhibitors stimulate renal phosphate reabsorption and calciuria, resulting in increased FGF23 and PTH and a reduction in active vitamin D. Although hyperparathyroidism and vitamin D deficiency could provoke adverse effects on bone, overall such effects have not been convincingly demonstrated. Moreover, available data indicate no significant correlation between FGF23 levels and BMD or fracture risk [47].

In the absence of consistent evidence, we advise to consider the possible adverse bone effects in vulnerable patients, such as the elderly and patients with diabetic kidney disease. However, given the prominent cardio-renal benefits of SGLT2 inhibitors, these drugs should currently not be withheld based on reports on biomarkers of bone health.

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Conflicts of interest

There are no conflicts of interest.

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